Valproate encephalopathy and hyperammonaemia

In their excellent review of non-hepatic hyperammonaemia, Hawkes and colleagues acknowledged the diverse modes of presentation of, and the importance of a high index of suspicion for, encephalopathy secondary to raised blood ammonia concentration. We would like to complement their review by reporting the case of a 78 year old woman with valproate encephalopathy associated with hyperammonaemia.

The patient presented to the accident and emergency department with a four week history of acute on chronic confusion, altered personality, and uncharacteristic aggressive behaviour. She had been taking sodium valproate (modified release) 500 mg twice daily and 300 mg at night, in addition to carbamazepine (modified release) 400 mg twice daily, for epilepsy diagnosed 20 years earlier.

On examination, her temperature was 37.5°C. The patient was confused, extremely agitated, and uncooperative. Physical examination was otherwise unremarkable.

Full blood count, renal, liver and clotting profiles were normal on admission. In addition, the random blood level of carbamazepine was 8 mg/l (therapeutic range 4–10 mg/l) and valproate was 80 mg/l (therapeutic range 60–100 mg/l). Computed tomography of the head did not reveal any intracranial space occupying lesion or haemorrhage. Examination of the cerebrospinal fluid was unremarkable. Nevertheless, the patient was started empirically on acyclovir treatment for presumed herpes simplex encephalitis.

Over the subsequent three days, the patient’s level of agitation became extreme and a neurological opinion was requested. The diagnosis of valproate encephalopathy was suspected and a blood ammonia concentration confirmed hyperammonaemia (174 μmol/l, normal range 0–39 μmol/l). Within 24 hours of discontinuing the sodium valproate, the patient’s aggression and agitation resolved and her level of confusion improved. The blood ammonia fell to 39 μmol/l 11 days after stopping the sodium valproate, and the patient was eventually discharged home on an increased dose of carbamazepine alone (600 mg twice daily) for treatment of her epilepsy.

Since 1979, there have been at least 30 cases of sodium valproate associated encephalopathy reported in the specialist neurological and pharmacological literature, however, only two reports have appeared in the general medical literature in English. It is important and potentially reversible cause of encephalopathy, and should be suspected in any confused patient on sodium valproate therapy.

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References
artery (above), the superior cerebellar artery (below), and the posterior communicating artery (parallel) deserve further comments, especially when clinicians are faced by an acquired isolated third nerve palsy in adults. As the pupillary fibres in the third cranial nerve are located dorsally and peripherally, a dilated pupil is frequently an early sign of a compressive lesion. An aneurysm at the junction of the posterior communication artery and internal carotid artery is a common cause. Actually, around 30% of all third nerve palsies are caused by aneurysms, especially posterior communicating aneurysms. Other causes include compression or infarction by neoplasms, infections, large dolichoclastic vessels, or shifted supratentorial structures. Occasionally it may be seen in generalised polyneuropathy (Miller-Fisher variant).  

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References  

Failure to develop diabetic ketoacidosis in a newly presenting type 1 diabetic patient  
In a recent issue of the journal McNulty and Hardy published a very interesting case history on the failure to develop diabetic ketoacidosis in a newly presenting type 1 diabetic patient. Their third self assessment question was “Why may be the explanation for this profoundly unwell patient with type 1 diabetes and hyperglycaemia not to have developed diabetic ketoacidosis?” The authors’ explanation is “because her insulinopenia was offset by her hypoadrenalism”. However, in patients with diabetic hyperglycaemic hyperosmolar syndrome (without ketoacidosis, as in the authors’ patient) increased concentrations of adrenal hormones are usually found. This makes the authors’ explanation very improbable. On the other hand, Schade and Eaton pointed out in 1977 (their p 596) that “insulin deficiency per se may not alone cause ketoacidosis.” An illustration of this problem is in the paper by Burge et al: they compared two groups of diabetic patients, with lower and higher hyperglycaemia. Ketone bodies were higher in the group with lower blood glucose. In uncomplicated diabetes mellitus, increased amounts of 34 organic acids have been identified; it is not known whether they are insulin dependent or not. Nevertheless, they cause severe acidosis, for example, a blood pH of 6.85 was found in the patient of Vernon and Postellon in absence of acetocetic and β-hydroxybutyric acids. Therefore, the authors should also ask: What are the exact mechanisms and details of development of both ketoacidosis and acidosis without ketone bodies in diabetic patients?  

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References  

A Disease Once Sacred.  

Written by two Australian epileptologists this book follows the historical concepts of epilepsy, ranging from mythological early views of the supernatural to the modern concepts of pathophysiology and treatment. Part I is a short outline of the present understanding of epilepsy including definition and classification. Parts II, III, and IV cover the clinical manifestations of epilepsy, the nature of the epileptic process and remedies, each examined from a historical viewpoint.  

Some ancients believed in the influence of bodily humours in triggering seizures, while others felt that sufferers from this malady had supernatural powers or were influenced by spirits or demons. Gradually, however, the concept of epilepsy as an illness with an underlying organic process began to be accepted along with a better comprehension of the origins and mechanisms of epileptic activity within the brain. The influence of Hughlings Jackson and the gradual acceptance of his views by his contemporaries makes particularly interesting reading.  

With regard to treatments for epilepsy the early remedies are discussed; this is followed by reference to the diversity of the effectiveness of bromide, more recent drug treatments and, ultimately, the evolution of the “designer” drugs. A major feature of the text is the liberal use of historical quotations supplemented by an extensive historical bibliography. Overall this
book provides a fascinating trip through history, following our understanding of this intriguing condition through to the present state of knowledge. It is recommended to anyone with an interest in the history of medicine and of epilepsy in particular.

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DIARY

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8–12 July 2002, University of Warwick, Coventry, UK. The course intends to develop understanding of the epidemiological principles of vaccine programme design, including serological surveys, parameter estimation, transmission dynamic models, and cost-effective analysis of different programmes. For further information contact Dr Stephen Hicks, Department of Biological Sciences, University of Warwick, Coventry CV4 7AL, UK (tel: +44 (0)2476 523540, fax: +44 (0)2476 523701, email: s.j.hicks@warwick.ac.uk).

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